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(54) Title: A LINKER AND A METHOD OF CHEMICAL SYNTHESIS

(57) Abstract: The present invention provides dockable linkers (10) for solid phase synthesis. These linkers (10) would allow reactions to be conducted in homogeneous solution but still allow easy isolation and purification of reaction products at each step of a synthetic route. The process would also allow easy analysis of all intermediates generated.

A LINKER AND A METHOD OF CHEMICAL SYNTHESIS

The present invention relates to a linker for chemical synthesis and a method of synthesising a chemical product. The chemical synthesis of the invention can be any technique where a chemical is altered, modified or changed and includes chemical, biochemical and physical modifications.

Solid phase synthesis techniques have revolutionised peptide and oligonucleotide synthesis and now routinely allow the preparation of biomolecules that would be inconceivable using traditional solution phase chemistry. Solid phase techniques are now being employed for the synthesis of other types of organic compounds and applied to drug discovery, N.K. Terrett, Combinatorial Chemistry, 1988, Oxford University Press.

Solid supports are used in synthetic chemistry research, where the molecule under construction is anchored to the solid support. This will allow more efficient and high yielding reaction sequences to be carried out.

Additionally small scale chemistry has the benefits of being economical, safe and environmentally friendly.

Solid supports are used in a wide range of chemical processes. The major advantages of using a solid support are that compounds can be easily isolated by simple filtration and washing procedures, and enabling large excesses of reagents to be used to drive reactions to completion.

One of the primary disadvantages of solid phase supports is that intermediates and products are difficult to characterise while the intermediates and products are still attached to the support. Various techniques have been applied to overcome this problem, notably Fourier Transform Infra-Red (FTIR) spectroscopy of resin bead samples and magic angle solid state NMR spectroscopy. Another technique used to tackle this problem is the use of soluble polymers thus allowing samples to be removed during a reaction sequence and analyzed in solution.

Another disadvantage of solid phase chemistry is that reactions rates can vary at different sites on a polymer support. The micro-environment around each substrate molecule can vary. Where a site is hindered and not easily accessible to reagent molecules incomplete reaction can occur giving rise to failure sequences. Extra capping reactions are often necessary to block failure products in order to prevent the failure products from interfering in later reactions.

It is generally accepted that chemical reactions proceed best when conducted in homogeneous solution. One approach adopted to mimic solution phase chemistry whilst maintaining the advantages of using a solid support has been the development of long chain spacer groups which hold the substrate molecule far away from the surface of the support and allow it to behave nearly as if it were in free solution.

Another approach is the so-called resin capture approach described by Keating T.A., *et al* J.Am.Chem.Soc., 1996: 118, 2574 to combinatorial synthesis where a solid support is

used to isolate products after solution phase chemistry has been carried out. Further processing of the captured material would have to take place under conventional solid phase conditions. Thus the resin capture method only allows convenient screening or analysis of the final product of the solution phase chemistry and thus has limited use in combinatorial chemistry where the analysis of intermediate products is often necessary.

The development of new linkers for attaching substrate molecules to solid phase supports is vital for the continuing growth and development of this technique.

The present invention seeks to provide a linker for chemical synthesis and a method of performing chemical synthesis.

According to a first aspect of the present invention there is provided a linker for solid phase synthesis comprising: a first part arranged to be fixed to a solid support and having a docking station; and a second part arranged to be linked to a molecule of interest and having a dockable region, wherein the dockable region is arranged to be selectively fixed to the docking station and selectively released therefrom by a predetermined stimulus.

The present invention thus provides a linker which allows a product or intermediary of a synthesis reaction (hereinafter a 'substrate molecule') to be attached to a solid support for e.g. isolation and purification. The inventive linker also provides means by which the substrate molecule can be selectively released from the solid support to allow e.g. solution phase chemistry to be conducted.

Preferably, the dockable region is arranged to be fixable to the same or another docking station after being released from the docking station. It is most unlikely that the same pairing of first and second parts would occur after separation. It is further contemplated that the first part of the linker could be entirely replaced after the second parts have been selectively released therefrom. The used first parts may be regenerated or sent to waste. This is advantageous as it ensures that there is minimum contamination between reaction stages. Further the new first parts may be isolatable in an alternative manner to the used first parts. Additionally or alternatively the new first parts may utilise a different predetermined stimulus to be selectively separated from the second part compared to the used first parts. Clearly this can be very beneficial depending upon the nature and stability of the reaction conditions being employed in different synthetic steps and substrate molecules that are formed therein.

The docking station may advantageously comprise a first ligand coordinatable to a metal, and the dockable region comprises a second ligand coordinatable to the metal, wherein the first and second parts are fixed together by both of the ligands being coordinated to the metal and at least one of said ligands becomes disassociated from the metal for said selective release. The use of a coordinated metal centre is preferred for a number of reasons, such as the availability of a number of different ligands which vary in strength of attachment and stimuli for release. Additionally said at least one ligand is reversibly dissociated from said metal. The at least one complex may be dissociated from said metal by stimuli selected from: chemicals; photochemical process; thermal process;

molecular recognition processes; electrostatic interactions; photolysis, heat and magnetic interaction.

Advantageously, one or both ligands are coordinated to said metal by: specific hydrogen bonding interactions; biological molecular interactions; base pairing in oligonucleotide binding; protein-small molecule interactions; antibody-antigen recognition; or to form a paramagnetic transition metal complex.

Other means of fixing the first and second part together are also possible, which each have advantages in particular synthetic schemes. The docking station and the dockable region are selectively fixed together by means of:

(a) coordination complexes where the docking station and/or the dockable region comprises a ligand which coordinate with a metal;
(b) charge transfer and/or Π-Π stacking interactions;
(c) hydrogen bonding interactions;
(d) steric interactions;
(e) covalent binding
(f) combination of two or more of the above.

When the fixing is via a metal centre coordinated to ligands on the first and/or second parts, the ligand may be selected from the group consisting of: porphyrins; tetrapyrrolic ligands; unidentate ligands; macrocyclic ligands; salen complexes or other related complexes; polyhistidine-iminodiacetic acid ligands.

Normally, both of the docking station and the dockable region comprise ligands, and the ligands coordinate to the metal. In these circumstances it is preferred that the

ligand comprising the docking station is more strongly fixed to the metal than the ligand comprising the dockable region. In this way the metal will not interfere with subsequent synthetic steps. This may be accomplished, e.g. by the dockable region comprising a unidentate ligand and/or the docking station comprises as multidentate ligand or at least a ligand with more coordination sites to the metal than the dockable region.

In the case where the selective fixing is by the charge transfer and/or Π-Π stacking interactions formed between the docking station and the dockable regions, it is preferred that one of the docking station and dockable region is electron rich and the other is an electron deficient species. For example the docking station and/or the dockable region may be a charged species.

The charge transfer and/or Π-Π stacking interactions may be formed between an electron deficient and electron rich molecular species, such as a rotaxane. The electron deficient species is selected from the group consisting of; aromatic, pseudoaromatic and heteroaromatic species having at least one nitro, cyano, phosphonate, sulphonate or carboxylate group. Preferably, the electron rich species is selected from the group consisting of aromatic, pseudoaromatic and heteroaromatic species having at least one alkyl, hydroxyl, alkoxyl, amino and substituted amino groups.

In the case where the selective fixing is by means of hydrogen bonding, the hydrogen bonding interactions are preferably between: (a) a N-H or OH group and a C=O, P=O, S=O or C=N group; such as (b) pyridinone and related

heterocyclic type H-bonding; and the interactions between DNA, RNA and mimetic analogues.

In the case where the selective fixing is by means of steric interactions, preferably the steric interaction is of the type either (a) where the shape of the docking station or the dockable region is permanently formed in the polymer matrix in production to fit with the shape of other one of the docking station or dockable region for example molecularly imprinted polymers; (b) where the interaction is protein-like or like other bio-chemical steric interactions, for example antibody antigen binding..

In the case where the selective fixing is by means of covalent binding, the covalent binding is preferably between Carbon-Nitrogen, Carbon-Oxygen or Carbon-Sulphur such as activated amide or ester groups. Preferably, the covalent binding is selectively releasable on reaction with a nucleophile. In addition reduction of a weak bond would be employed to cleave the linkage, such as N-N and N-O.

It is important for the wide applicability of the invention that linkers may be produced that are selectively released under the influence of a number of different stimuli. For example the first part is selectively separated from the second part by stimuli selected from: chemicals; photochemical process; thermal process; molecular recognition processes; electrostatic interactions; change in pH; and magnetic interaction.

The chemical which forms the initial compound includes, but is not restricted to: biochemicals, organic chemicals, inorganic chemicals, peptides, polypeptides, polymers,

nucleic acids, antibodies, expression vehicles, or biological entities such as cells.

In this invention, the solid phase includes, but is not restricted to: polymer beads, glass, bead, magnetic particles, particulates, irregular solid materials, colloidal materials, porous materials, membranes, meshes, plates, columns, the surface of a reaction or storage vessel such as vials and tubes of which the surfaces may be coated with a polymer or a surface reactive compound.

According to a second aspect of the present invention there is provided a method of synthesising a chemical product comprising the steps of:

(a) having a first part of a linker attached to a solid support;

(b) attaching an initial compound to a second part of the linker;

(c) conducting a reaction or reactions to the attached initial compound of step (b) to form an intermediate compound attached to the second part of the linker;

(d) isolation of the intermediate compound attached to the solid support via the linker;

(e) releasing the second part of the linker from the first part of the linker by means of a predetermined stimulus.

The synthetic route thus enjoys the benefits of the synthetic reaction steps that can be performed in homogeneous solution if desired and the benefits enjoyed by utilising a solid phase for simple isolation and purification and the other benefits of solid phase synthesis.

Preferably, step (e) further includes analysing or characterising said intermediary product. This is advantageous as the solid support is not present and so does not interfere with the analysis. This is normally very difficult when using a solid phase and may even be destructive to the particular substrate molecule investigated or prevent further synthetic steps being performed thereon.

Advantageously, the method further includes the step (f) of conducting a further reaction or reactions on the intermediate compound.

The method will normally include the further step (g) of selectively fixing the said second part to a said first part. Optionally, the method further includes step (h) isolating the product of step (g) attached to a solid phase via the linker. Steps (a) to (f) are normally repeated until a desired chemical product is produced. The second aspect of the invention allows the testing, analysis and isolation of all intermediary products which really enhances the practicality of the stepwise synthetic approach.

The present invention will now be explained in more detail in relation to specific examples and with the aid of the accompanying drawings, in which:

Fig. 1 illustrates the general synthetic method of the present invention;

Fig. 2 illustrates a first embodiment of the linker of the present invention;

Fig. 3 illustrates a preferred embodiment of the second

part of the linker of the present invention;

Fig. 4 illustrates the preparation of preferred coordination complexes for use in the present invention;

Fig. 5 illustrates the preparation of further preferred coordination complexes for use in the present invention;

Fig. 6 illustrates a further second illustrated embodiment of the linker of the present invention; and

Fig. 7 illustrates a synthetic method according to a preferred embodiment of the present invention.

Figure 1 shows a general reaction scheme for a synthetic approach utilising the present invention. The present invention thus provides a system of linkers which can be used to reversibly anchor a substrate molecule to a solid support, such as a resin bead, any polymeric support or a suitably treated surface. Hereinafter the linkers of the invention shall often be referred to as 'dockable linkers' to convey the essence of the linker which is the first and second parts of the linker may be selectively joined together (docked) or released from one another.

Figure 1 shows a linker 10 comprising a first part 12 and a second part 14. The first part 12 is attached to a resin bead 20, but of course this could be any type of solid support. The second part 14 is attached to an initial compound A of a substrate molecule 22 via a moiety L. As is clear from Figure 1 the first and second parts 12, 14 are joined together at regions spaced from, respectively, the solid support 20 and the substrate molecule 22.

In Figure 1, step (a) shows the linker 10 with the first and second parts 12, 14 fixed together. The first part 12 is provided with a docking station 16 via which it is fixed a dockable region 18 of the second part 14.

As shown by step (b), the first part 12 may be selectively separated from the second part 14 under the action of a predetermined stimulus as described in more detail below. A sample may be removed for analysis if desired.

As shown by step (c) the substrate molecule 22 may be subjected to further processing steps, normally in a solution phase, to further build the substrate molecule 22. In step (c) the substrate molecule has now obtained a part B and so the substrate molecule 22 is now compound AB.

The substrate molecule 22 may then be re-attached to a solid phase 20 as shown if step (d). In the illustrated embodiment a similar first part 12 and solid support 20 is used as shown in step (a). This is a matter of choice and the solid phase 20 and/or the first part 12 may be different to those of step (a). It is, of course, necessary that the dockable region 18 is dockable to the chosen docking station 16 and so it is normal for the docking stations 16 at least remain in the same general class of docking stations 16. However, the rest of the first part 12 and the solid phase 20 is likely to be varied for compatibility with later processing steps.

After re-fixing the substrate 22 to the solid support 20, the substrate will normally be purified and/or isolated as shown in step (e).

Steps (b) to (e) will be repeated until the substrate 22 has the desired properties, e.g. particular functionality, geometry, steriochemistry, bioactivity, etc.. As shown in step (f), in the illustrated embodiment this is compound ABCDE.

Thereafter the desired compound ABCDE forming substrate 22 will normally be cleaved from the linker by severing the bond to moiety L of the second part as shown in step (g). Substrate molecule 22 can then be subjected to testing and analysis as desired, step (h).

When anchored the substrate molecule 22 can be treated e.g. to allow simple isolation and purification. The substrate molecule can be detached from the support when desired to allow e.g. solution phase chemistry to be carried out thereupon.

As will be clear from the foregoing, at the conclusion of each reaction step, the reaction mixture is again exposed to the solid support 20 bearing the first part 12 having a complimentary binding group 16 for the second part 14 of the linker 10. The substrate molecules 22 with the second part 14 of the linker 10 are thus bound to the solid support 20 selectively. The solid support 20 then allows a simple purification cycle where the substrate 22 can be washed free of excess reagents and by-products.

It will be clear that the invention allows large excesses of reagents to be employed in reactions helping to drive them to completion, but reaction steps can be carried out in homogeneous solution with the advantage of increased reaction rate, etc. Also the problem of failure sequences

generated by incomplete reaction due to the hindered nature of some of the reaction sites on the polymer is largely avoided.

Samples of the reaction solution can also be removed at any stage of the synthetic route for analysis by mass spectrometry or NMR spectroscopy allowing the reaction sequence to be monitored easily. The linker 10, or often just the second part 14 thereof, will normally be designed so that it exhibited minimum interfering signals itself in the NMR spectrum or other analysis procedure. The linker 10 is also designed so that it was compatible with the reagents used during the reaction sequence.

As shown by the general scheme of Figure 1 for synthesis employing the dockable linkers 10 of the invention, the invention provides all the advantages of solid support synthesis combined with the advantages of solution phase reaction to improve the overall efficiency of the synthetic route.

A number of approaches to the selective fixing and release of the first and second parts 12, 14 of dockable linkers 10 can be envisaged. These include the use of coordination complexes where a ligand is reversibly dissociated from a metal on the first part 12 attached to the support 20 either chemically or photochemically, and molecular recognition processes (Rebek J., Acc. Chem. Res., 1990, 399; Zimmerman S.C. *et al*, J. Org. Chem., 1992, 57, 2215; Zofar A. *et al*, Tetrahedron Lett, 1996, 37, 2327) such as specific hydrogen bonding interactions which could be dissociated thermally. These could be based on biological molecular interactions such as base pairing in

oligonucleotide binding, protein-small molecule interactions or antibody-antigen recognition. Alternatively physical processes could be employed such as electrostatic or magnetic separation of the first and second parts 12, 14, for example using a paramagnetic transition metal complex. Charge transfer and/or Π-Π stacking interactions could also be used.

Figure 2 illustrates the use of 2,2':6',2"-terpyridine complexes of iron II 30 (or other metals e.g. zinc II) to form a connection between one terpyridine 32 forming the docking station 16 attached to the solid support 20 and another 34 forming the dockable region 18 of the second part 14 and attached to the substrate molecule 22 under construction.

Terpyridine ligands have been chosen for the illustration as they are robust compounds and stand up to a range of reaction conditions that might be applied to the substrate molecule 22.

The complexes 32, 34 can be dissociated by adding another ligand to displace one terpyridine or by altering the oxidation state of the metal 36. Conversion of iron II to iron III renders the complex unstable due to the smaller size of iron II and the terpyridine 34 would dissociate. In the illustrated embodiment the metal will be retained by the ligand 32 attached to the support 20. It would be undesirable if the metal 36 leached from the support 20 as this would require replacing before binding to the dockable region 18 could again occur and the metal 36 may interfere with the next reaction step to be performed.

In order to ensure that the metal 36 remained coordinated to docking station 16, it is possible to use a weaker ligand such as the diimidazolylpyridine 34' shown in Figure 3 as the dockable region 18 rather than the terpyridine ligand of Figure 2. Such ligands have a weaker affinity for metals than terpyridine due to the wider bite angle of the three coordination nitrogen atoms.

The use of the weaker ligand as the dockable region 18 thus ensures retention of the metal by the docking station e.g. formed by the terpyridine 32 bound to the solid support 20. The diimidazolylpyridines 34' may be synthesised using the Wallach cyclisation of oxamide derivatives 40 to construct the imidazole rings of this ligand 34'.

If the diimidazolylpyridines 34' are used as the dockable region 18, the diimidazolylpyridines forms the entire second part with the chlorine atoms in this ligand providing a point of attachment for the substrate 22.

Other types of transition metal complex may also be used. for example cyclopentadienyl complexes where a ligand can be dissociated photochemically. Photochemical release of the first and second parts 12, 14 has the advantage that no other chemical reagents are needed that could otherwise disrupt the substrate 22 and/or which may interfere with the subsequent reaction step and/or which would need to be removed before reaction could take place.

A method for attacking the substrate to the terpyridine could employ 4'-azidoterpyridine 42 shown in Figure 4. This compound 42 may also be employed in construction of a first or second part 12, 14 such as the phosphoramidate 44

by reaction with phosphite esters.

As shown in Figure 5, N-terpyridyl aziridine 50 can also be used as the docking station 16 or the dockable region 18. Compound 50 can be used to link a photolabile nitrobenzyl group via the phenolic OH group of compound 52 to form compound 54 which can act as a second part 14. The photolabile group would function as a release mechanism to allow dissociation of the final product from the linker when synthesis is complete.

Figure 5 illustrates a basic synthesis based on aldol type chemistry such as the Robinson annelation employing the derivative of 54 shown in Figure 5 as compound 56. The product is an unsaturated ketone 58 and this can be subjected to a variety of reactions such as acylation, protection, and further aldol reactions as desired.

Figure 6 illustrates the use of specific hydrogen bond recognition between complimentary heterocyclic compounds. In the embodiment illustrated in Figure 6, one heterocycle component such as the melamine derivative 60 is attached to the solid support 20 and another such as the cyanuric acid derivative 62 is used as the second part 14 to carry the substrate molecule 22. This heterocyclic pair is chosen because it is known to form tight binding complexes (similar complexes stable at 10uM) and has been investigated by extensively by Whitesides *et al*, J. Am. Chem. Soc., 1993, 115, 1330. The compounds 60, 62 are stable and easy to prepare and should stand up to a wide range of reaction conditions that might be applied during the synthetic sequence applied to the substrate molecule 22. The compounds 60, 62 will not be compatible with all

possible reagents e.g. strong bases and powerful oxidising or reducing agents but could be employed in syntheses employing fairly mild or neutral reaction conditions.

The link between molecules 60, 62 can be broken thermally by heating the system to circa 90°C which results in separation of the two heterocycles shown schematically in Figure 6. Alternatively the complex could be disrupted by adding a polar solvent with a high dielectric constant e.g. DMF or DMSO although this might not be desirable for the subsequent reaction step. The process can be considered almost analogous to the polymerase chain reaction used to amplify DNA sequences in molecular biology where complimentary DNA strands are melted to cleave the duplexes and to allow the next cycle of reaction by the thermostable DNA polymerase to proceed. In the synthetic case once the linker 10 has been cleaved, the solid support 20 can be removed (e.g. by filtration or the solution pumped into a different reaction chamber) and the solution containing the substrate molecules 22 bound to the second part 14 of the linker 10 can be then treated with the desired reagents at an appropriate temperature to effect the next transformation.

It is preferred for the binding affinity of the heterocyclic pair to be very high to ensure near quantitative recovery of the second part 14 at each step. If the binding constant is too low, even small losses at each cycle of reaction would accumulate and lead to intolerably low yields after only a few reaction steps. If necessary further binding units could be incorporated into the dockable linker to increase binding affinity and specificity as shown schematically as 66 in Figure 6.

The present invention provides dockable linkers 10 for solid phase synthesis. These linkers 10 would allow reactions to be conducted in homogeneous solution but still allow easy isolation and purification of reaction products at each step of a synthetic route. The process would also allow easy analysis of all intermediates generated.

The above description concentrates on two specific strategies for the selective fixing and release of the first and second parts 12, 14. However, the invention can be carried out using any suitable reversible linkage and the choice of the exact linkage will be dependent upon the present synthesis to be conducted and the preference of the skilled person.

Figure 7 illustrates the use of the linker 10 of Figure 6 in carrying out Diels Alder cycloadditions; reactions which can be effected without the need for additional acid or base catalysts or redox reagents which could damage the binding group of the linker 10. Reaction of a linker bound unsaturated ester such as 72 with a number of dienes e.g. 74 to give Diels Alder products 76. Further inverse electron demand Diels Alder reaction would generate 78.

CLAIMS:

1. A linker for solid phase synthesis comprising: a first part arranged to be permanently fixed to a solid support and having a docking station; and a second part arranged to be linked to a molecule of interest and having a dockable region, wherein the dockable region is arranged to be selectively fixed to the docking station and selectively released therefrom by a predetermined stimulus.

2. A linker according to Claim 1, wherein the dockable region is arranged to be fixable to the same or another docking station after being released from the docking station.

3. A linker according to Claim 1 or Claim 2, wherein the docking station comprises a first ligand coordinatable to a metal and the dockable region comprises a second ligand coordinatable to the metal, wherein the first and second parts are fixed together by both of the ligands being coordinated to the metal and at least one of said ligands becomes disassociated from the metal for said selective release; and optionally said ligand or ligands are coordination complexes.

4. A linker according to Claim 3, wherein said at least one complex is reversibly dissociated from said metal.

5. A linker according to Claim 3 or Claim 4, wherein the at least one ligand is dissociated from said metal by stimuli selected from: chemicals; photochemical processes; thermal processes; molecular recognition processes; electrostatic interactions; microwaves; acoustic means;

andand magnetic interaction.

6. A linker according to Claim 5, wherein one or both complexes are coordinated to said metal by: specific hydrogen bonding interactions; biological molecular interactions; base pairing in oligonucleotide binding; protein-small molecule interactions; antibody-antigen recognition; or to form a paramagnetic transition metal complex.

7. A linker according to any one of the preceding claims, wherein the docking station and the dockable region are selectively fixed together by means of:

(a) coordination complexes where the docking station and/or the dockable region comprises a ligand which coordinate with a metal;
(b) charge transfer and/or Π-Π stacking interactions;
(c) hydrogen bonding interactions;
(d) steric interactions;
(e) covalent binding
(f) combination of two or more of the above.

8. A linker according to Claim 7, wherein the ligand is selected from the group consisting of: porphyrins; tetrapyrrolic ligands; unidentate ligands; macrocyclic ligands; salen complexes or other related complexes; polyhistidine-iminodiacetic acid ligands.

9. A linker according to Claim 8, wherein both of the docking station and the dockable region comprise ligands, and the ligand both coordinate to the metal.

10. A linker according to Claim 9, wherein the ligand

comprising the docking station is more strongly fixed to the metal than the ligand comprising the dockable region.

11. A linker according to any one of Claims 7 to 11, wherein the dockable region comprises a unidentate ligand.

12. A linker according to any one of Claims 7 to 11, wherein the docking station comprises as multidentate ligand.

13. A linker according to any one of Claims 7 to 12, wherein the charge transfer and/or Π-Π stacking interactions are formed between the docking station and formed between the docking station and the dockable regions, wherein one of the docking station and dockable region is electron rich and the other is electron deficient species.

14. A linker according to Claim 13, wherein docking station and/or the dockable region is a charged species.

15. A linker according to Claim 13 or Claim 14, wherein the charge transfer and/or Π-Π stacking interactions are formed between rotaxanes, and related structures.

16. A linker according to any one of Claims 13 to 15, wherein the electron deficient species is selected from the group consisting of; aromatic, pseudoaromatic and heteroaromatic species having at least on nitro, cyano, phosphonate, sulphonate and carboxylate groups.

17. A linker according to any one of Claims 13 to 16, wherein the electron rich species is selected from the

group consisting of aromatic, pseudoaromatic and heteroaromatic species having at least one hydroxyl, alkoxyl, amino and substituted amino groups.

18. A linker according to any one of claims 7 to 17, wherein the hydrogen bonding interactions are between: (a) a N-H or OH group and a C=O, P=O, S=O or C=N group; and/or (b) pyridinone and related heterocyclic type H-bonding; and/or the interactions between DNA, RNA and PNA molecules.

19. A linker according to any one of Claims 7 to 18, wherein the steric interaction is of the type either (a) where the shape of the docking station or the dockable region is permanently formed in the polymer matrix in production to fit with the shape of other one of the docking station or dockable region such as molecularly imprinted polymers; and/or (b) where the interaction is protein-like or like other bio-chemical steric interactions.

20. A linker according to any one of Claims 7 to 19, wherein the covalent binding is between Carbon-Nitrogen, Carbon-Oxygen or Carbon-Sulphur and activated amide or ester groups.

21. A linker according to any one of Claims 7 to 20, wherein the covalent binding is selectively releasable on reaction with a nucleophile, or ther reagent.

22. A linker according to according to any one of the preceding Claims, wherein the first part is selectively separated from the second part by stimuli selected from: chemicals; photochemical; thermal; molecular recognition

processes; electrostatic interactions; change in pH; and magnetic interaction.

23. The linker according to any one of the preceding claims, wherein the molecule of interest is selected from: biochemicals; organic chemicals; inorganic chemicals; peptides; polypeptides; polymers; nucleic acids; expression vehicles; antibodies; or biological entities such as a cells.

24. A method of synthesising a chemical product comprising the steps of:

(a) having a first part of a linker attached to a solid support;

(b) attaching an initial compound to a second part of the linker;

(c) conducting a reaction or reactions to the attached initial compound of step (b) to form an intermediate compound attached to the second part of the linker;

(d) isolation of the intermediate compound attached to the solid support via the linker;

(e) releasing the second part of the linker from the first part of the linker by means of a predetermined stimulus.

25. A method according to Claim 24, wherein step (e) further includes analysing or characterising said intermediary product.

26. A method according to Claim 24 or Claim 25, further including step (f) conducting a further reaction or reactions on the intermediate compound.

27. A method according to Claim 24, Claim 25 or Claim 26, further including the step (g) selectively fixing the said second part to a said first part.

28. A method according to Claim 27, further including the step (h) isolating the product of step (g) attached to a solid phase via the linker.

29. A method according to all of Claims 26 to 28, wherein steps (f) to (h) are repeated until a desired chemical product is produced.

30. A method according to any one of claims 24 to 29, wherein the initial compound is selected from the group consisting of: biochemicals; organic chemicals; inorganic chemicals; peptides; polypeptides; polymers; nucleic acids; expression vehicles; antibodies; or biological entities such as a cells.

31. A method according to any one of Claims 24 to 30, wherein the linker of anyone of Claims 1 to 23 is used in said method.

32. A linker as hereinbefore described, with reference to and/or as illustrated by the accompanying drawings.

33. A method of producing a compound as hereinbefore described with reference to and/or as illustrated by the accompanying drawings.

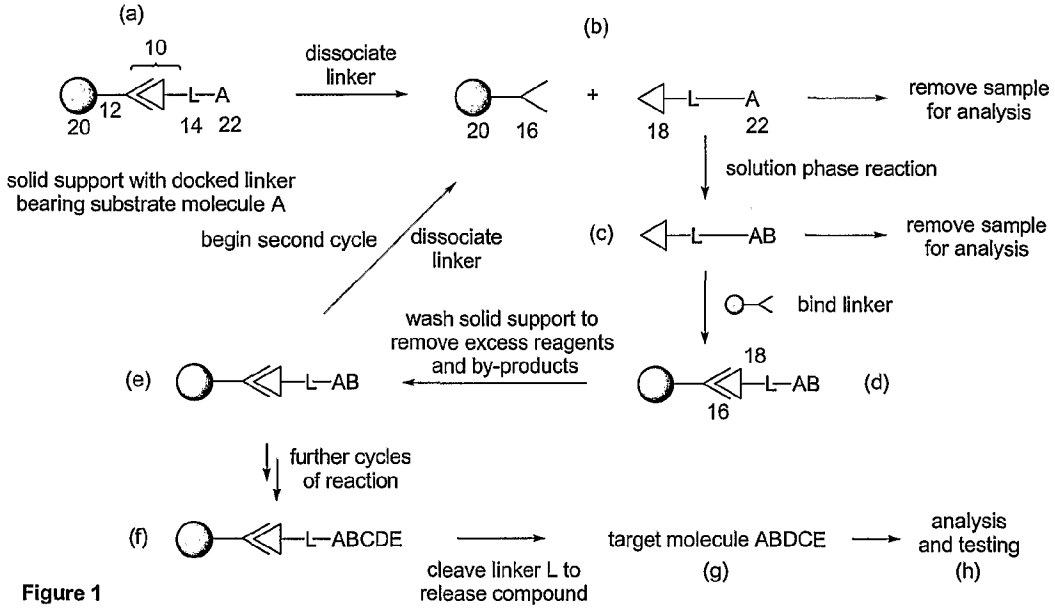

Figure 1

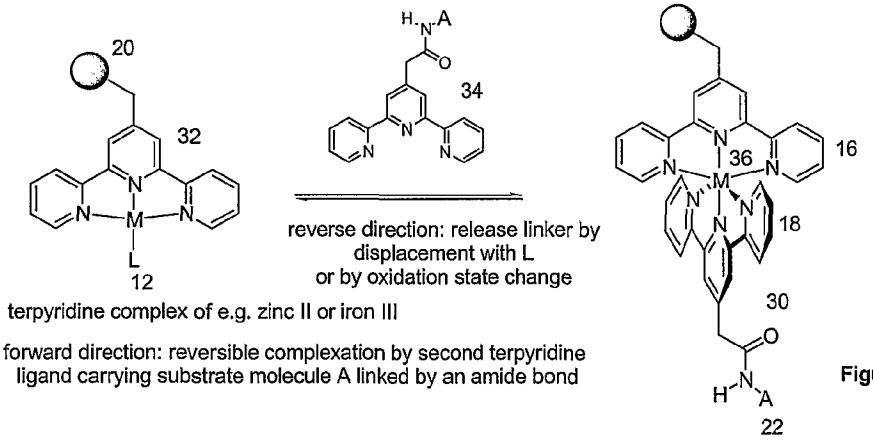

Figure 2

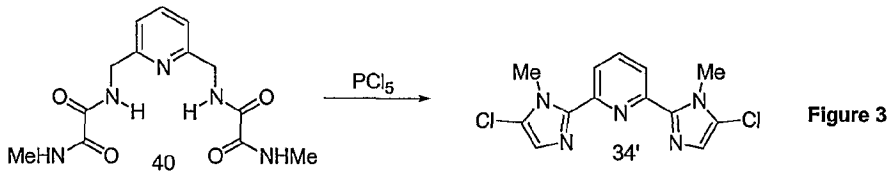

Figure 3

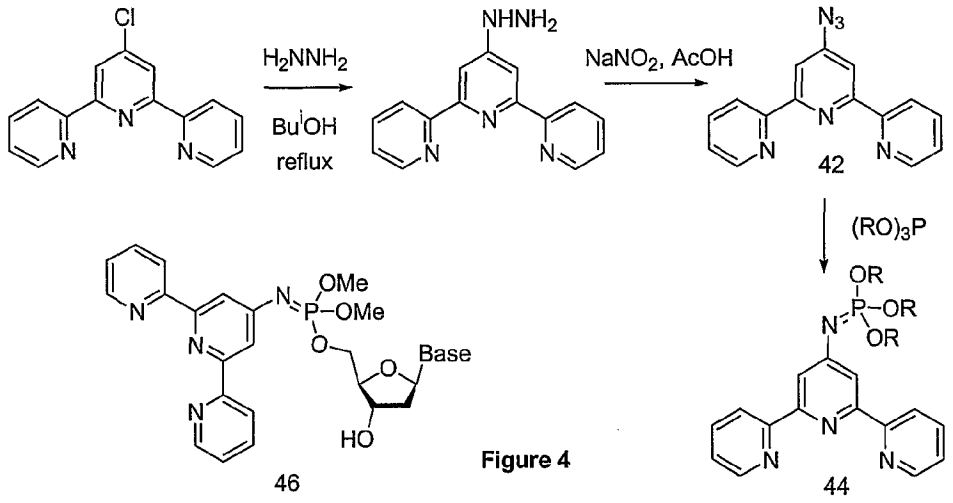

Figure 4

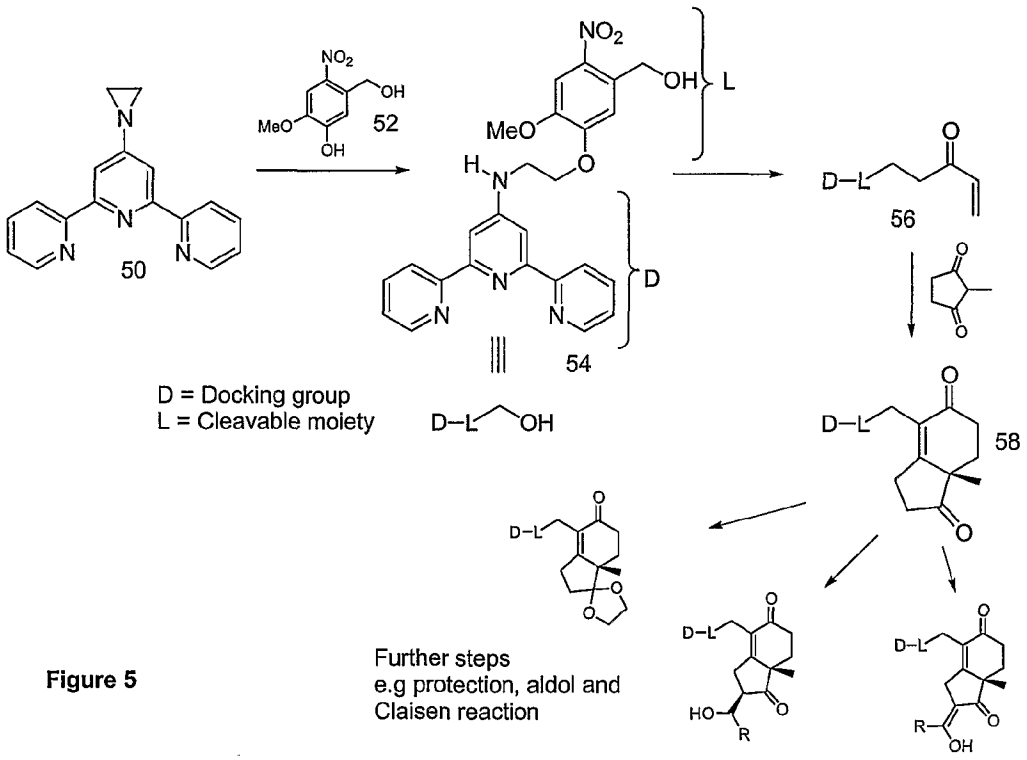

Figure 5

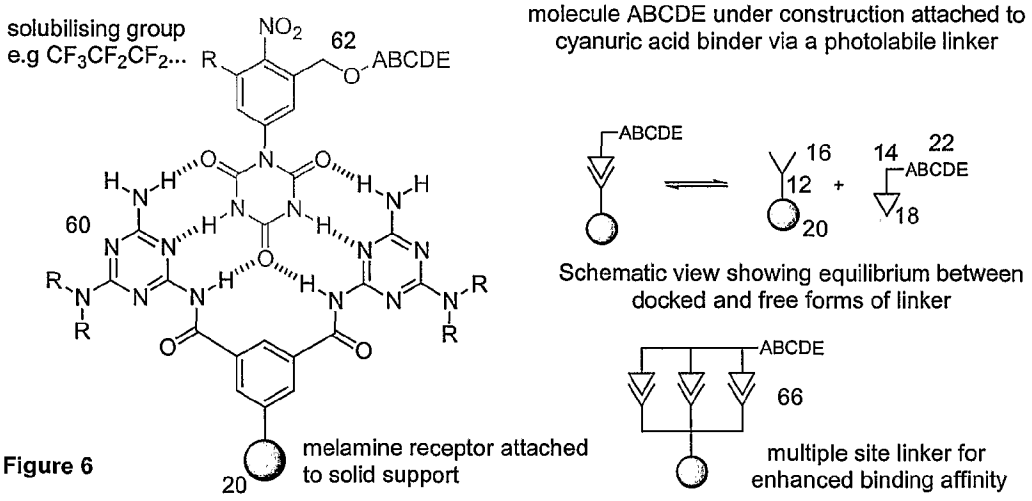

Figure 6

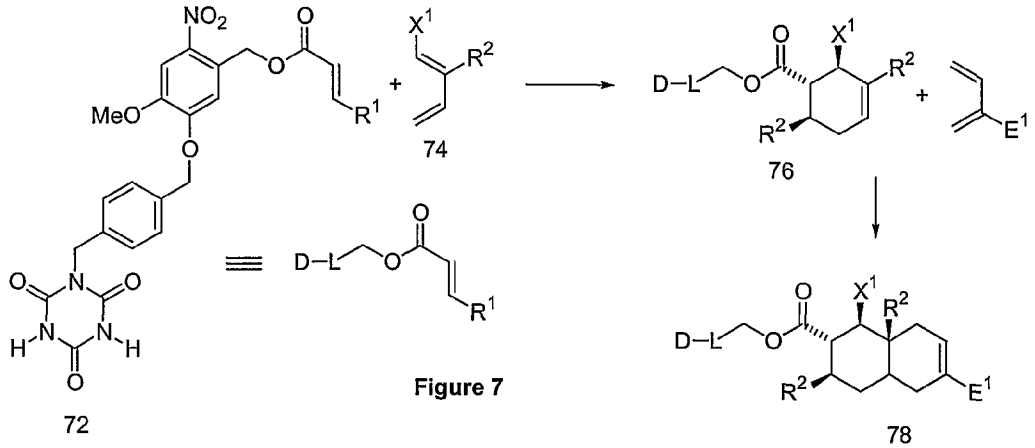

Figure 7